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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

KIRCHER, William, B.
Shook, Hardy & Bacon L.L.P.
One Kansas City Place
1200 Main Street
Kansas City, MO 64105-2118
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year)
16 February 2000 (16.02.00)

Applicant's or agent's file reference
DCW/SH

IMPORTANT NOTIFICATION

International application No.
PCT/IB99/00088

International filing date (day/month/year)
07 January 1999 (07.01.99)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address

KIRCHER, William, B.
Shook, Hardy & Bacon L.L.P.
One Kansas City Place
1200 Main Street
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United States of America

State of Nationality | State of Residence

Telephone No.
816 474 6550

Facsimile No.
816 471 5547

Teleprinter No.

3. Further observations, if necessary:
An agent has been appointed.

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Dominique DELMAS

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994) 003111115

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 29 May 2000 (29.05.00)	
International application No. PCT/IB99/00088	**Applicant's or agent's file reference** DCW/SH
International filing date (day/month/year) 07 January 1999 (07.01.99)	**Priority date** (day/month/year) 08 January 1998 (08.01.98)
Applicant PHILLIPS, Jeffrey, Owen et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

05 August 1999 (05.08.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Dominique DELMAS
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

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NOTIFICATION CONCERNING
AMENDMENTS OF THE CLAIMS

(PCT Rule 62 and
Administrative Instructions, Section 417)

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as International Preliminary Examining Authority

Date of mailing (day/month/year)	
02 May 2000 (02.05.00)	
International application No.	International filing date (day/month/year)
PCT/IB99/00088	07 January 1999 (07.01.99)

Applicant

CURATORS OF THE UNIVERSITY OF MISSOURI et al

The International Bureau hereby informs the International Preliminary Examining Authority that no amendments under Article 19 have been received by the International Bureau (Administrative Instructions, Section 417).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Olivia RANAIVOJAONA

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year)
02 May 2000 (02.05.00)

International application No.
PCT/IB99/00088

IB 99

ference

International filing date (day/month/year)
07 January 1999 (07.01.99)

12

ear)
(08.01.98)

Applicant
PHILLIPS, Jeffrey, Owen et al

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

08 May 1999 (08.05.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
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Facsimile No.: (41-22) 740.14.35

Authorized officer
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CUMP68854	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB99/00088	International filing date *(day/month/year)* 07 JANUARY 1999	Priority date *(day/month/year)* 08 JANUARY 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): A61B 5/02 and US Cl.: 600/309		
Applicant CURATORS OF THE UNIVERSITY OF MISSOURI		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [X] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05 AUGUST 1999	18 OCTOBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer ERIC F. WINAKUR
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0858

Form PCT/IPEA/409 (cover sheet) (July 1998)*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Internati nal application No.
PCT/IB99/00088

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-7 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the claims:
pages NONE , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages 8-10 , filed with the demand
pages NONE , filed with the letter of _____

☒ the drawings:
pages 1, 2 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IB99/00088

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	4, 6, 7, 10, 11, 14, 15	YES
	Claims	1-3, 5, 8, 9, 12, 13	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-15	NO
Industrial Applicability (IA)	Claims	1-15	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1 - 3, 5, 8, 9, 12, and 13 lack novelty under PCT Article 33(2) as being anticipated by Miller et al. Miller et al. teach a method, and apparatus for monitoring local cerebral physiology, including pH. Without providing limitations regarding "predicting the outcome", Miller et al. will be held to meet the limitations of the claims.

Claims 4, 6, 7, 10, 11, 14, and 15 lack an inventive step under PCT Article 33(3) as being obvious over Miller et al. Miller et al. teach that their device is used for assessing physiological processes, but do not teach the specific assessments set forth in the claims. Without a showing of unexpected results or criticality, it would have been obvious to one of ordinary skill in the art at the time of the invention to use Miller et al. in typical medical situations, such as those set forth in the claims.

---------- NEW CITATIONS ----------
NONE

VIII. Certain observations n the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1 - 5 and 8 - 15 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because the claims are indefinite for the following reason(s):
Claim 1, although the claim is drawn to a method of "predicting" none of the claimed steps limit the claim to this scope.
Claim 8, although the claim is drawn to an apparatus for "predicting" none of the claimed elements limit the claims to this scope.
Claims 10-15, although the claims are drawn to a "use" they do not clearly set forth method steps.

PCT/IB99/00088
IPEA/US 24 MAY 2000

CLAIMS:

1. A method of predicting the outcome of head trauma comprising monitoring at least one characteristic of cerebrospinal fluid (CSF) on the brain with time within the initial 24 hours following trauma.

2. A method of claim 1 wherein a change of at least one characteristic of CSF is monitored within the initial 48 hours following trauma.

3. A method of claim 1 wherein at least one characteristic of CSF is monitored with a probe received in a ventricle of the patient.

4. A method of claim 1 wherein the measured characteristic is compared with a base line correlating with brain death.

5. A method of claim 1 wherein said monitored characteristic is selected from the group consisting of pH, temperature, CO_2 concentration and partial oxygen pressure.

6. A method of treating head trauma, comprising the steps of:

   i. monitoring the change of at least one characteristic of cerebrospinal fluid on the brain with time within the initial 24 hours following trauma; and

ii. managing the patient such that the characteristic of the cerebrospinal fluid adjusts to be within normal parameters with time.

7. A method of claim 6 wherein said monitored characteristic is selected from the group consisting of pH, temperature, CO_2 concentration and partial oxygen pressure.

8. Apparatus for predicting the outcome of head trauma, the apparatus comprising:

a) a probe for reception in a patient's brain ventricle and capable of monitoring at least one characteristic of CSF;

b) means for calculating at least one CSF characteristic at the probe at sequential times;

c) means for comparing the calculated values with stored values; and

d) means for displaying and/or recording the resulting values.

9. An apparatus of claim 8 wherein said probe is capable of monitoring a CSF characteristic selected from the group consisting of pH, temperature, CO_2 concentration and partial oxygen pressure.

10. The use of the measured changes of at least one characteristic of CSF with time in diagnosis or therapy of neurological injuries.

AMENDED SHEET

PCT/IB99/00088
IPEA/US 24 MAY 2000

11. The use of claim 10 wherein said CSF characteristic is selected from the group consisting of pH, temperature, CO_2 concentration and partial oxygen pressure.

12. The use of means for monitoring the change of at least one CSF characteristic over time in the manufacture of apparatus for diagnosing the outcome of blunt head trauma.

13. The use of claim 12 wherein said CSF characteristic is selected from the group consisting of pH, temperature, CO_2 concentration and partial oxygen pressure.

14. The use of means for monitoring the change of at least one CFS characteristic with time in the manufacture of apparatus for the therapy of blunt head trauma.

15. The use of claim 14 wherein said CSF characteristic is selected from the group consisting of pH, temperature, CO_2 concentration and partial oxygen pressure.

AMENDED SHEET

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61B 5/02

A1

(11) International Publication Number: WO 99/34730

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(30) Priority Data:
9800370.0 8 January 1998 (08.01.98) GB

(71) Applicant *(for all designated States except US)*: CURATORS OF THE UNIVERSITY OF MISSOURI [US/US]; 316 University Hall, Columbia, MO 65211 (US).

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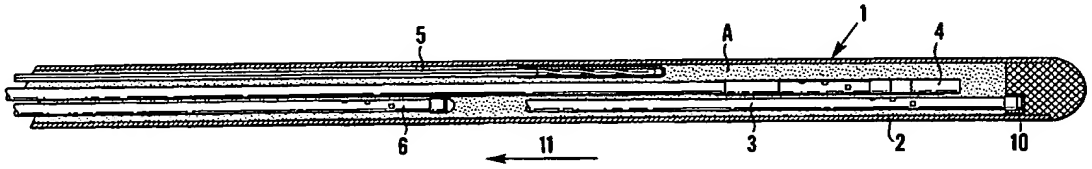
(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: METHOD AND APPARATUS FOR MONITORING CEREBRAL PHYSIOLOGY



(57) Abstract

A method, and apparatus for predicting the outcome of head injury trauma by monitoring the pH of cerebrospinal fluid (CSF). The apparatus includes a pH probe (3) for reception in a patient's brain ventricle, and capable of monitoring the pH of CSF; calculator for calculating the pH at the probe at sequential times; a comparator for comparing the calculated pH values with stored values, a device for displaying and/or recording the resulting values.

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METHOD & APPARATUS FOR MONITORING CEREBRAL PHYSIOLOGY

This invention relates to a method and apparatus for monitoring the cerebral cellular environment, especially in patients who have sustained brain injury.

In the event of medical incidents, such as severe trauma to the head, it is frequent practice to monitor the intracranial pressure (ICP) in a ventricle of the brain. An increase in ICP is thought to be indicative of secondary injury such as brain swelling, and it is known to be necessary to relieve pressure by draining cerebrospinal fluid (CSF) if a patient's ICP rises above a critical level. While a body of data exists in the management of intracranial hypertension there have been few investigations of the significance of other cerebral physiological parameters.

The present invention is based on this observation that the pH of CSF is an indicator of the condition of a patient's brain after suffering head trauma and thus the likely outcome of medical treatment.

According to one aspect of the present invention there is provided a method of predicting the outcome of head trauma which comprises monitoring the pH of cerebrospinal fluid (CSF) and comparing the measured pH with a base line representing brain death.

In investigations which have been carried out by the present inventors, a pH sensor was inserted into a cerebral ventricle of a patient and the pH monitored by sequential measurements. Both the rate of change of pH and the absolute level of pH were measured on a continuous basis. While a rapid decrease of pH is a strong indicator of a poor survival prognosis, the absolute value of pH can be used directly to provide a guide to the patients' well being. In general, it has been found that stable levels of pH in the region of 7.15 to 7.25 suggest that the patient is likely to improve clinically, while significantly lower pH levels or continuously falling pH levels are a pointer to poor survival chances. In one case, a pH of about 7.05 correlated with brain stem death.

The present invention also includes apparatus for monitoring the pH and optionally other cerebral physiological parameters which comprises a lumen adapted for introduction through an opening in a skull of a living patient into a cerebral ventricle, said lumen having a pH sensor therein and permitting CSF to flow thereinto and over the sensor.

Preferably, the pH sensor contains a pH-sensitive colour change or fluorescent material and the colour change or fluorescence is measured optically by determining the absorption of a standard light beam.

The catheter containing the pH probe may be a single lumen and may also be used for removing samples of CSF fluid from the ventricle. Alternatively, a bi-lumen catheter may be employed in which the sensor is housed in one lumen and CSF is withdrawn from the other lumen. Removal of CSF may be desirable because of a perceived increase in ICP or may be removed prior to a detected increase in ICP because of a predicted deterioration in the patient's well being because of a fall in pH.

The invention is illustrated by reference to the accompanying drawings in which:-

Figure 1 is a section through a tubular probe containing various sensors;

Figure 2 is a part section through the probe;

Figure 3 is a schematic view showing one way in which the apparatus may be connected to a patient;

Figure 3A is an enlarged view of the Luer lock; and

Figure 3B is a partial section through the patient's head showing one method of introducing the lumen containing the pH sensor.

Referring to the drawings the apparatus comprises a tubular probe (1) comprising a microporous sheath which permits the transfer of CSF into a gel (A) filling the probe. A number of sensors are housed within the tubular probe. One of these is a pH sensor (3). Sensor 3

comprises a length of optical fibre having a mirrored distal end 10 to reflect light back towards the proximal end 11, longitudinally of the optical fibre. Several holes (12) are laser drilled through the optical fibre in a number of random directions normal to the longitudinal axis of the fibre. These holes are filled with a gel containing a phenol red dye which undergoes a colour change with change in pH. A colour change over the pH range from about 6.8 to 7.8 is desirable. The colour shade of the phenol red indicator is determined by passing a light beam along the optical fibre and measuring the absorption spectrum of the reflected beam. After calibration, the absorption spectrum of the reflected beam gives a measure of the pH of the CSF.

As indicated in Figure 1, the tubular probe may also include other sensors such as a CO_2 concentration sensor (pCO_2), 4, a partial oxygen pressure sensor (pO_2), 6, and a thermocouple 5.

Tubular probe 1 is introduced into a ventriculostomy catheter 21 which has a distal end having a foraminous wall to permit CSF to flow into and around the tip of the probe.

The catheter may be introduced into the patient's skull and retained in place with a tubular skull bolt, e.g. as shown in U.S. Patent 4 903 707 (the contents of which are specifically incorporated herein by reference). Conveniently, the catheter is urged into the opening in the

skull as shown schematically in Figure 3 until expression of CSF indicates that the catheter tip has reached the cerebral ventricle.

Referring to Figure 3, the catheter 21 has a distal end into which the tip of the probe is positioned. In the Example illustrated, the catheter comprises a single lumen, e.g. of PVC or polypropylene. The catheter is connected via a Luer lock to an extension tube 13 which may incorporate a side port (not shown) for sampling CSF and monitoring ICP. The extension tube is further connected by optical fibres to a detection, monitoring and display equipment.

Apparatus which is commercially available for intravascular blood monitoring under the registered trade mark 'Paratrend' 7 (Diametrics Medical Ltd 5, Manor Court Yard, Hughendon Ave, High Wycombe, HP13 5RE, United Kingdom) may be adapted for monitoring the pH of CSF by providing means for holding the sensor lumen in place in the skull. This may involve a bolt as described in the above cited US patent 4903707 or secured by other fixing means as indicated in Figure 3B. Referring to this latter Figure it can be seen that the catheter 21 is fixed to the patient's head by securing means 14, passes under the scalp in contact with the skull 15 and then through an opening in the skull and brain 16 to reach a brain ventricle 17. The small, size and flexibility of the catheter (about 2-3 mm diameter) facilitates introduction of the

catheter. The distal tip of the catheter is provided with holes to permit flow of CSF therethrough and around the tip of the probe which is also located within the cerebral ventricle.

Example

16 patients admitted to hospital following brain trauma resulting in severe brain injury (GCS $\leq$ 8) were included in the study. A 'Paratrend 7' sensor measuring pH, pCO_2 and pO_2 was advanced into a ventriculostomy. Sensor data was stored into a computer and transferred to a spreadsheet, pH, pCO_2, pO_2, 1CP, CPP, patent manipulation and outcome were monitored.

Six patients were excluded due to technical difficulties in obtaining and recording data early in the study.

Four patients were found to have initial pH in the range 7.15 to 7.22 but had progressive CSF acidemia over the next 24 to 48 hours. All progressed to herniation and brain death. Clinical evidence of brain death occurred as the pH approached 7.05.

Two patients were found to have a relative high initial CSF pH in the range 7.20-7.25. These values remained substantially constant and both patients remained vegetative.

In the remaining four patients initial pH was in the range 7.12 to 7.24 but increased over the following 48 hours. All displayed significant clinical recovery.

It was found that patient care activities and other known stressors were found to cause a rapid decrease in CSF pH which resolved shortly after the activity stopped. All negative changes in brain pH occurred significantly before elevations of ICP or change in CPP could be detected. This suggests that CSF pH is a more effective indicator of a patient's neurological condition since remedial action can be taken earlier. It was also noted that measurement of CSF pH provides a means for monitoring cerebral ischemia following blunt head trauma. Falling pH correlates to ongoing cellular injury and occurs well before increases in intracranial pressures.

CLAIMS:-

1. A method of predicting the outcome of head trauma comprising monitoring the pH of cerebrospinal fluid (CSF) with time within the initial 24 hours following trauma.

2. A method of claim 1 wherein a change of CSF pH is monitored within the initial 48 hours following trauma.

3. A method of claim 1 wherein the pH of CSF is monitored with a pH probe received in a ventricle of the patient.

4. A method of claim 1 wherein the measured pH is compared with a base line correlating with brain death.

5. A method of treating head trauma, comprising the steps of:

i. monitoring the change of cerebrospinal fluid pH with time within the initial 24 hours following trauma; and

ii. managing the patient such that the pH rises with time.

6. Apparatus for predicting the outcome of head trauma, the apparatus comprising:

a) a pH probe for reception in a patient's brain ventricle and capable of monitoring the pH of CSF;

b) means for calculating the pH at the probe at sequential times;

c) means for comparing the calculated pH values with stored values; and

d) means for displaying and/or recording the resulting values.

7. The use of the measured changes of CSF pH with time in diagnosis or therapy of neurological injuries.

8. The use of means for monitoring the change of CSF pH over time in the manufacture of apparatus for diagnosing the outcome of blunt head trauma.

9. The use of means for monitoring the change of CSF pH with time in the manufacture of apparatus for the therapy of blunt head trauma.

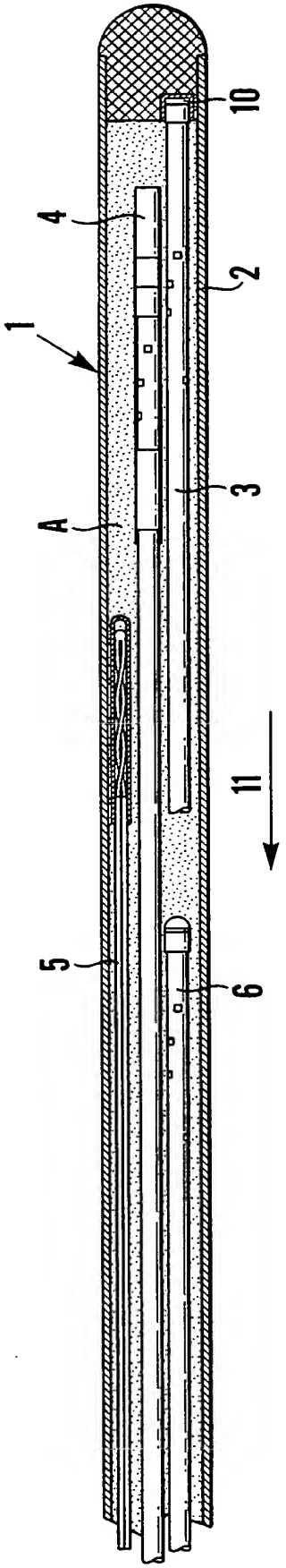

Fig.1

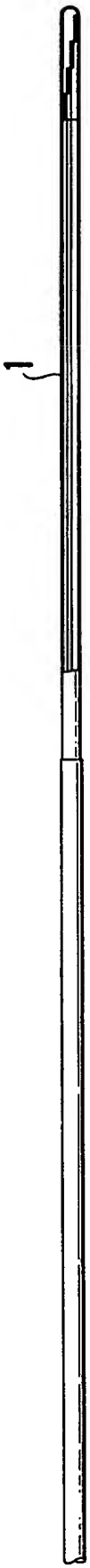

Fig.2

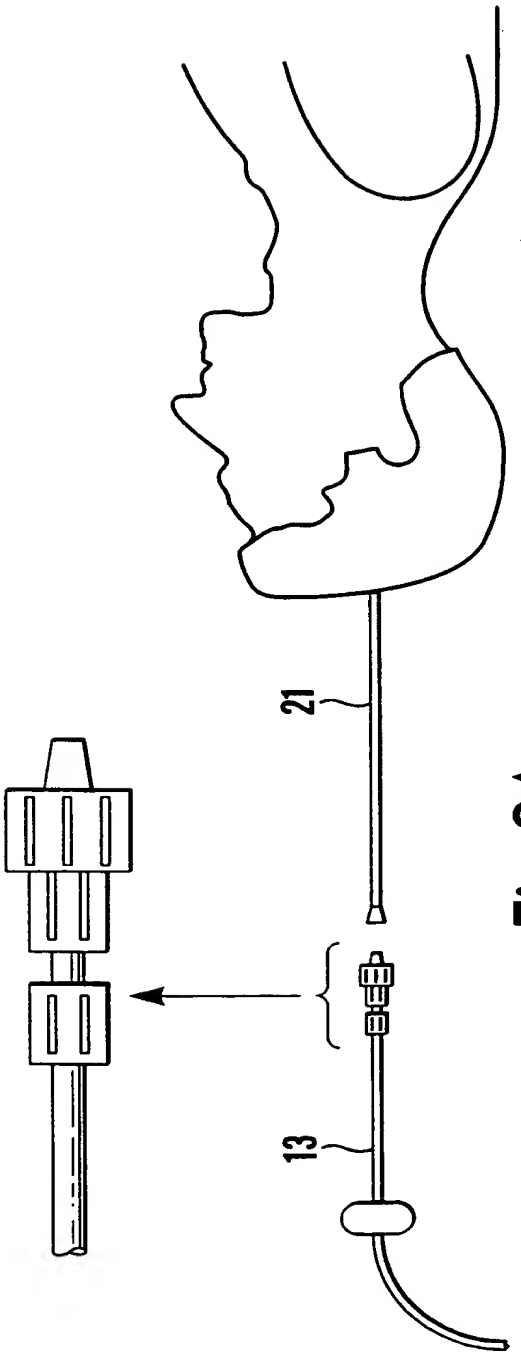

Fig.3A

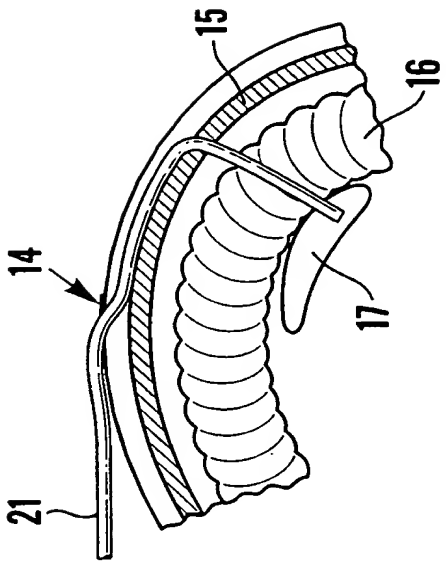

Fig.3B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB99/00088

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61B 5/02
US CL :600/309
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 600/309, 361, 378

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,579,774 A (MILLER et al) 03 December 1996, col. 13 lines 27-29.	1-3, 6 --- 4, 5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 05 APRIL 1999	Date of mailing of the international search report 27 APR 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ERIC F. WINAKUR Telephone No. (703) 308-3940

Form PCT/ISA/210 (second sheet)(July 1992)*